The Use of a Dynamic Compression Intramedullary Nail for Tibiotalocalcaneal Arthrodesis

Study Protocol & Statistical Analysis Plan

NCT03780452

July 21, 2020

Ashish Shah, MD, Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

The Use of a Dynamic Compression Intramedullary Nail for Tibiotalocalcaneal Arthrodesis

Version Date: July 21, 2020

Principal Investigator:

Ashish B. Shah, MD
Associate Professor of Orthopedic Surgery and Director of Clinical Research
University of Alabama at Birmingham

Study Sponsor:
MedShape, Inc

Study Location:
University of Alabama at Birmingham (UAB)
Department of Orthopaedic Surgery
1313 13th Street South
Birmingham, Alabama 35205

Principal Investigator Signature

_____ _____
Ashish B. Shah, MD Date

Study Summary

Title:
The use of a dynamic compression intramedullary nail for tibiotalocalcaneal arthrodesis

Purpose:
The purpose of this study is to determine the clinical efficacy of a novel dynamic compression intramedullary nail for tibiotalocalcaneal (TTC) arthrodesis.

Design
This is a prospective, single-group study. Patients of UAB who are scheduled to undergo TTC arthrodesis will be screened for eligibility and informed consent will be obtained from those who meet the inclusion/exclusion criteria. Subjects will be assessed pre-operatively and then at several post-operative intervals: 2 weeks, 6 weeks, 12 weekss, 24 weeks, and 1 year. A CT scan will be obtained at the 24-weeks interval.

Population:
The study population will consist of up to 30 subjects from UAB who meet the following criteria:

Inclusion Criteria:

- Meets indications for TTC arthrodesis and receives the DynaNail implant
- Able to understand the requirements of the study, provide a written consent, and willing to comply with the study protocol
- 18 years of age or older

Exclusion Criteria:

- Investigator determines that the subject is unlikely to comply with the requirements of the study
- Non-English speaker
- Blind
- Illiterate
- Prisoner

Outcome Parameters:
The following information will be collected at study visits:

- Pain using a 100mm Visual Analog Scale (VAS)
- Short form-36 (SF-36)
- Foot and Ankle Ability Measure (FAAM)

Purpose of the Study:
The purpose of this study is to determine the clinical efficacy of a novel dynamic compression intramedullary nail for tibiotalocalcaneal (TTC) arthrodesis.

Background & Significance: Arthritis of both the ankle (tibiotalar) and subtalar (talocalcaneal) joints (Figure 1) is debilitating due to severe pain and loss of function. Unfortunately, the only conservative treatment option is bracing which often fails to relieve pain and the decision to perform surgery is subsequently made. The only surgical option is to perform a fusion (arthrodesis) of both of these hindfoot joints. This procedure is called a tibiotalocalcaneal arthrodesis and involves preparing these joint surfaces by removing the arthritic cartilage until healthy bleeding bone is obtained, allowing the body to "glue" the bones together. TTC arthrodesis is an orthopedic procedure with nearly 30,000 operations performed annually at a cost of approximately $32,000 per procedure [1]. Non-union is the most severe complication, with reported non-union rates as high as 50% [2-5]. Patients with conditions such as diabetes mellitus and Charcot neuroarthropathy and behaviors such as chronic smoking are at a particularly high risk for non-union [3, 6-10]. If a non-union is left untreated, irreversible damage can occur and revision arthrodesis or amputation are the only remaining treatment options.

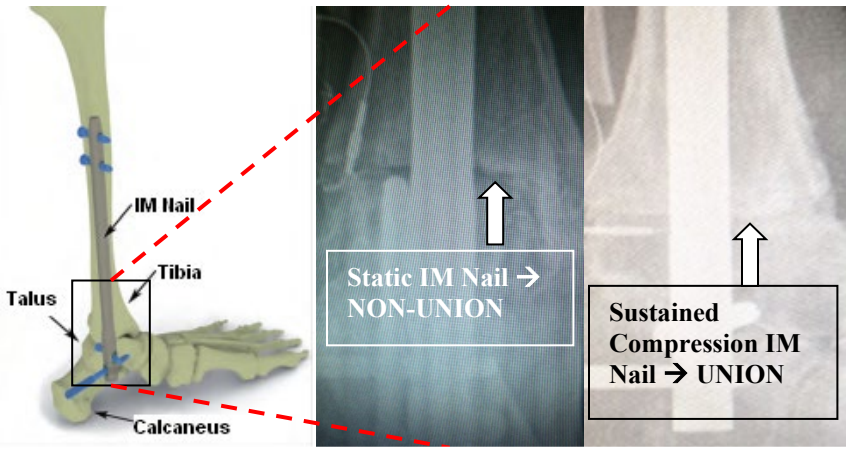

Figure 1. (left) IM nail fixation of TTC joints. (middle) Non-union 16 weeks post static IM nail fixation. (right) Bony fusion 6 weeks post dynamic sustained compression nail fixation.

However, the body can take several months to a year to achieve union and therefore, internal support is mandatory. This is typically performed with an intramedullary (IM) nail (Figure 1) that is inserted through the bottom of the foot, traverses both joints, and is fixed to the shin bone (tibia). Additionally, in order to help the body achieve union faster, compression of the bone surfaces together is performed at the time of surgery. This is analogous to putting a clamp across two pieces of wood that have been glued together until the glue dries. With traditional intramedullary nails for a tibiotalocalcaneal arthrodesis, compression is manually obtained at the time of surgery [11]. However, this initial compression is lost soon after surgery as bone settling or resorption occurs at the joint spaces [12, 13]. If even 1 mm of bone resorption occurs at the joint interface, implanted nails loosen and as a result require a second procedure to provide additional compression [7, 8]. Therefore, it would be ideal to have a medical device that both stabilizes the tibiotalocalcaneal arthrodesis and provides dynamic compression to accommodate the bone resorption that occurs after surgery [14].

The DynaNail is a tibiotalocalcaneal arthrodesis intramedullary nail that allows for compression at the time of surgery and has a nitinol (pseudoelastic memory metal [15-17]) element that is

stretched to a lengthened state during the surgical procedure and slowly contracts to its resting state after the surgical procedure to provide dynamic sustained compression while bone resorption is occurring at the ankle and subtalar joints [7]. In addition to dynamic sustained compression, the DynaNail also provides torsional stability and load-sharing capacity absent in traditional IM nails. To date, minimal clinical data is available to evaluate the effects of sustained compression via IM nail on TTC arthrodesis, particularly in high-risk patients with challenging pathologies [11, 18, 19].

This study's immediate impact on human health is the use of a novel medical device to understand how sustained compression influences joint arthrodesis, especially in the presence of bone resorption. By having a more fundamental understanding of the mechanobiology of clinical TTC arthrodesis, this study's longer term impact on human health will be the design of more efficient medical devices that would fuse joints over shorter time periods and in cases of detrimental pathology where non-union would otherwise occur.

Design & Procedures:
This proposal is a collaborative effort between UAB and MedShape, Inc. This is a prospective investigation to assess the clinical outcomes of patients with a tibiotalocalcaneal arthrodesis with the Dynamic Compression Intramedullary Nail (DynaNail). We are planning on enrolling 30 patients. No placebo control will be used, as there is no other IM nail available capable of providing sustained compression. Additionally, given that many patients receiving this treatment have had prior failed treatments and face poor alternatives such as amputation, using a prior-generation IM nail as a control treatment would be unethical.

Subject Recruitment:
Patients of UAB with end-stage tibiotalar (ankle) and talocalcaneal (subtalar) joint arthritis from any etiology will be eligible to enroll in the study. In general, tibiotalar and subtalar arthritis is caused by trauma. Traumatic injuries have no predilection for race, religion, cultural background, etc. Therefore, all demographic groups will have access to this study and should be represented.

Selection of Subjects:
Patients will be identified in the clinic by an attending orthopaedic foot and ankle surgeon or his physician assistant based on clinical exam and radiographic findings. Patients will be screened for eligibility by the research coordinator/ key personnel in close coordination with the surgeon.
The following inclusion criteria will be used:

- Meets indications for TTC arthrodesis and receives the DynaNail implant
- Able to understand the requirements of the study, provide a written consent, and willing to comply with the study protocol
- 18 years of age or older

The following exclusion criteria will be used:

- Investigator determines that the subject is unlikely to comply with the requirements of the study
- Non-English speaker
- Blind
- Illiterate

- Prisoner
- Pregnant women

Consent Process:
Upon determination that a subject is compatible with the eligibility criteria of the protocol, the study will be explained to the subject by the investigator or his/her authorized designee. If the subject indicates interest in participating in the study, the informed consent document will be provided to the patient, since this document provides a comprehensive explanation of the study in lay terms. If the subject continues to show interest, the investigator or his/her authorized designee will thoroughly explain to the subject the required elements of informed consent and all aspects of the study (i.e., inclusion/exclusion criteria, risks, benefits and alternatives to the study, etc.). The subject will receive a copy of the study consent form and the signed and dated original copy will be retained in the subject's study file. After the patient leaves the clinic building, the attending surgeon will be available to answer questions by phone. The process of obtaining informed consent will be in accordance with all applicable regulatory requirements (Federal Register Vol. 48, No. 17, 1982, pp 8951-2).

Pre-operative Questionnaire:
After informed consent, the patients will be asked to complete the following patient reported outcomes questionnaires: 100mm VAS for pain, Short form-36 (SF-36), and the Foot and Ankle Ability Measure (FAAM). They will then be scheduled for surgery in a routine fashion. These questionnaires are being done for this research only.

Surgery:
The following surgical procedure is standard of care. The surgical procedure will involve both tibiotalar and talocalcaneal joint preparation through any approach (lateral, posterior, anterior with sinus tarsi). The use of supplemental bone graft is at the discretion of the treating surgeon but must be documented. The MedShape DynaNail will then be inserted according to the manufacturer's technique. The patient will be placed in a short leg splint and kept non-weight bearing. The patient will be discharged from the hospital when medically ready.

Follow-Up Visits and Questionnaires:
The patient will return to clinic for visits at the following intervals after surgery: 2 weeks, 6 weeks, 12 weeks, 24 weeks, and 1 year. At each of these time points, the same patient specific outcome questionnaires will be administered: the 100mm VAS for pain, SF-36, and the FAAM. 3-view X-rays will be taken at each of these visits to assess the amount of travel of the compressive element. At 24 weeks post-op, a CT scan will be obtained to assess healing. Additionally, a radiographic and clinical follow-up form will be filled out at each of the following follow-up visits: 6 weeks, 12 weeks, 24 weeks, and 1 year. At 24 weeks and 1 year post-op, all X-ray images will be de-identified and burned to a CD/DVD, along with CT images at the 24 weeks time point. A summary of interventions and time points, and whether or not they are standard of care, is depicted in Table 1. MedShape will be responsible for payments of all non-standard of care items.

Table 1. Study Intervention Timeline

	Baseline	Surgery	2 weeks PO	6 weeks PO	12 weeks PO	24 weeks PO	1 year PO
Office Visit (with questionnaires*)	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Radiographic and Clinical Follow-Up Form			NS	NS	NS	NS	NS
3 view ankle xray	SOC	SOC	SOC	SOC	SOC	SOC	SOC
CT Scan						SOC	
Image deidentification						NS	NS
*VAS, FAAM, SF-36							
SOC - Standard of Care, NS - Not Standard of Care							

Subject Withdrawal:
Subjects may voluntarily withdraw from the study upon request. The investigator may withdraw a participant if he/she is unable or unwilling to participate in study follow-ups. The reason for withdrawal will be documented by research staff. Subjects that fail to schedule surgery, cancel surgery, or that do not receive the DynaNail will be considered to be screen failures and will be removed from the study and the study data.

Adverse Events:
Due to the observational nature of the study, only adverse events (AEs) that are serious, unexpected, and device-related will be recorded. AEs will be collected from the time that the study subject receives the DynaNail implant. All adverse events will be monitored and reported per UAB IRB policies.

Risk Assessment/ Surgery and Device-Related Risks –
Tibiotalocalcaneal arthrodesis is the standard of care for ankle and subtalar arthritis that has failed non-operative management. Patients enrolled in this study are receiving the standard of care surgical procedure and therefore there is no increased risk of the surgical procedure. While the DynaNail has an internal nitinol element, its basic features are the same as any other intramedullary nail that is available. It has screws that lock into the calcaneus and tibia as well as the ability to statically compress during surgery. The benefit of the added nitinol element is continued compression after surgery as bone resorption is occurring. No other device has this ability.

The only conceived risk is that the element does not function correctly and does not move or breaks. However, if one of these events happens, it simply turns the device into a standard intramedullary nail. MedShape is aware of zero instances in which a nitinol compressive element within a DynaNail has broken either during surgery or post-operatively, such that the likelihood of this occurring is very low. The Investigator team at UAB can help to minimize these risks by following guidance provided in MedShape's Instructions for Use that are included with every DynaNail device.

Data integrity and Patient Privacy Risks –
Any time information is collected, there is a potential risk of loss of confidentiality. Every effort will be made to keep patient information confidential; however, this cannot be guaranteed. To minimize these risks, data will be stored securely under the patient's study identification number. All clinical data, images and surgical/procedural data will be de-identified prior to any in-house or public presentation of data or images. Coded data will only be released to those listed as study investigators or support staff. Paper data records will be stored in locked file cabinets in a locked office. All electronic research data will be stored on the PI computer that is password protected

and encrypted. MedShape cannot provide an estimate of the likelihood of these risks, as it has no knowledge of any data or patient privacy breaches that may or may not have occurred at UAB.

Imaging-related Risks –
This study includes multiple imaging visits during the study. These tests or treatments involve a small amount of radiation. The radiation exposure from this research is about 60 microsievert. To give an idea about that amount of radiation, we will compare it to the amounts that people encounter in daily life. There is radiation that naturally occurs from space and from rocks in the soil. This natural radiation is greater at higher altitudes. This research gives about the same amount of radiation as you would get from living in a high-altitude city such as Denver for 4 days, or taking 1 airplane flight from New York to Los Angeles. The radiation dose is what patients will receive from this study only. Much of the imaging during this study falls under regular care for the condition, and would occur whether or not patients participate in this research. These studies will not add to the risk of the research.

Pregnancy-Related Risks –
Radiation exposure to a woman's reproductive organs may harm an embryo or fetus. Also, if radioactive materials are used for certain types of scans, harm may come to an embryo, fetus, or an infant who is breast feeding. To mitigate these risks, women of childbearing potential will undergo a urine pregnancy test and it must be negative before they can undergo x-rays. These patients will also be encouraged to tell their physician if they may be pregnant because the x-rays should not be done while they are pregnant. If they do become pregnant during this study, they must tell the researchers immediately.

Pregnancy tests performed during the early stages of pregnancy do not always reveal pregnancy. Therefore, to minimize these risks radiation exposure that includes the reproductive organs will be limited to the first ten days after a woman who can become pregnant has begun her most recent menstrual period. This is standard policy in clinics and hospitals within UAB. This policy applies unless there is an important medical reason requiring radiation outside this time frame.

Other Risks –
There may possibly be other risks or side effects that are unknown at this time. Patients concerned about other, unknown side effects, should discuss this with the researchers.

Institutional Review Board Approval
The study protocol, questionnaires, and consent forms will be submitted to the UAB IRB.

Patient Confidentiality
All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentiality. All paper records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number. Only de-identified data will be sent to MedShape. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the IRB.

Consent procedures and forms, and the communication, transmission and storage of patient data will comply with the UAB's IRB and GCP (good clinical practices) requirements for compliance

with The Health Insurance Portability and Accountability Act (HIPAA). All study personnel must complete training in the Protection of Human Subjects.

Costs to the Subject:
There will be no cost to the subjects. The non-standard of care items in Table 1 will be done solely for research and will be paid for by MedShape.

Subject Payments:
Subjects will be paid $500 in stipends - $200 at their 24 weeks visit and $300 at their 1 year visit.

Data Analysis & Statistical Considerations:
We aim to enroll 30 patients over a three-year period. The primary outcome is fusion. Preoperative and postoperative outcome questionnaire scores will be compared using paired t-tests. Preoperative and postoperative outcome questionnaire scores will be compared using a paired t-test. As the outcomes will be a comparison for the same patient, a paired t-test should be sufficient. As there is not a control nail group in this study, there is not a secondary/tertiary/etc. treatment group to compare to, which would potentially necessitate a more elaborate statistical comparison method such as ANOVA, etc. Sample size was determined based on that used in previous studies, both for the Duke and Coughlin Clinic DynaNail.

Data & Safety Monitoring:
As this is a minimal risk study, no data and safety monitoring (DSMB) will be used. Data will be managed using Microsoft Excel. Monitoring of study conduct and safety data will be conducted on an ongoing basis by Sponsor.

The following will be reported within 10 calendar days, except when 24-hour reporting is specified:

1. Information that indicates a change to the risks of potential benefits of the human research:
a. An interim analysis, safety monitoring report, publication in the literature, or revised investigator brochure that indicates an increase in the frequency or magnitude of a given harm, uncovers a new risk, or provides more information about the benefits of the human research.
b. Change in FDA labeling or withdrawal of the device from the market.
c. Protocol deviation that harmed participants or indicates participants might be at increased risk of harm. If the protocol deviation was made in order to eliminate an apparent immediate hazard to a participant, the PI must submit the information within 24 hours.
d. Complaint of a participant that indicates participants or others might be at increased risk of harm or at risk of a new harm.
2. Any adverse event experienced by a participant of other individual, which is both unexpected and at least probably related to the human research device.
a. A harm is “unexpected” when its specificity and severity are not accurately reflected in the consent document.
b. A harm is “at least probably related” if the research device more likely than not caused the harm.
c. Timeline Exception: If the unexpected and at least probably related harm is death of a research subject, the PI must report the information within 24 hours.
3. Finding of Non-Compliance or Allegation of Non-Compliance.

4. Protocol Deviations: Failure to follow the protocol due to the action or inaction of the investigator or research staff. Exception – If the protocol deviation was taken in order to eliminate an apparent immediate hazard to a participant, the PI must report the information within 24 hours.
5. Breach of confidentiality: must be reported within 24 hours.
6. Change to protocol taken without prior IRB review to eliminate an apparent immediate hazard to a participant: must be reported within 24 hours.
8. Complaint of a participant that cannot be resolved by the research team.
9. Unanticipated adverse device effect. Exception – if the unexpected and at least probably related adverse device effect results in the death of a research subject, the PI must report the information within 24 hours.

All data collected will remain confidential. Data will be stored securely under the patient's study identification number. All clinical data, images and surgical/procedural data will be de-identified prior to any in-house or public presentation of data or images. Coded data will only be released to those listed as study investigators or support staff. Paper data records will be stored in locked file cabinets in a locked office. All electronic research data will be stored on the PI computer that is password protected and encrypted.

IRB, FDA and any applicable regulatory agencies will have access to the study records upon request. The data and associated identifiers will be kept for up to 5 years in a locked research facility accessible only to designated personnel, at which time the data will be destroyed per hospital policy. If the results of this study are published, the data will be reported collectively without mention of any subject's identity, thereby ensuring subject anonymity.

Privacy, Data Storage & Confidentiality:
All data will be maintained and stored in accordance with HIPAA regulations. Any electronic documents containing identifiers, such as enrollment logs, will be password protected, not accessible by anyone other than members of the research team, and located on computers that require a system log-on and password. Any physical documents with identifiers, such as signed consent forms, will be stored in locked filing cabinets when not in use. Back-up devices, such as external hard drives, and patient questionnaires will also be kept in a locked filing cabinet.

Data from this study is confidential and will only be disclosed to certain parties upon request: the study sponsor, the UAB Institutional Review Board (IRB) and federal agencies with regulatory oversight such as, but not limited to, the Food and Drug Administration (FDA). All data sent to MedShape will be de-identified.

REFERENCES:

1. idata_Research_Inc, *US Market for Small Bone and Joint Orthopedic Devices.* 2009.
2. Jeng, C.L., et al., *Tibiotalocalcaneal arthrodesis with bulk femoral head allograft for salvage of large defects in the ankle.* Foot Ankle Int, 2013. **34**(9): p. 1256-66.
3. Caravaggi, C., et al., *Intramedullary compressive nail fixation for the treatment of severe Charcot deformity of the ankle and rear foot.* J Foot Ankle Surg, 2006. **45**(1): p. 20-4.

4. Chou, L.B., et al., *Tibiotalocalcaneal arthrodesis.* Foot Ankle Int, 2000. **21**(10): p. 804-8.
5. Kim, C., A.R. Catanzariti, and R.W. Mendicino, *Tibiotalocalcaneal arthrodesis for salvage of severe ankle degeneration.* Clin Podiatr Med Surg, 2009. **26**(2): p. 283-302.
6. Jehan, S., et al., *The success of tibiotalocalcaneal arthrodesis with intramedullary nailing--a systematic review of the literature.* Acta Orthop Belg, 2011. **77**(5): p. 644-51.
7. Yakacki, C.M., et al., *Pseudoelastic intramedullary nailing for tibio-talo-calcaneal arthrodesis.* Expert Rev Med Devices, 2011. **8**(2): p. 159-66.
8. Yakacki, C.M., et al., *Compression forces of internal and external ankle fixation devices with simulated bone resorption.* Foot Ankle Int, 2010. **31**(1): p. 76-85.
9. Perlman, M.H. and D.B. Thordarson, *Ankle fusion in a high risk population: an assessment of nonunion risk factors.* Foot Ankle Int, 1999. **20**(8): p. 491-6.
10. Dalla Paola, L., et al., *Use of a retrograde nail for ankle arthrodesis in Charcot neuroarthropathy: a limb salvage procedure.* Foot Ankle Int, 2007. **28**(9): p. 967-70.
11. Muckley, T., et al., *Biomechanical evaluation of primary stiffness of tibiotalocalcaneal fusion with intramedullary nails.* Foot Ankle Int, 2007. **28**(2): p. 224-31.
12. Muller, M., et al., *Manual of Internal Fixation*. 1995.
13. Eichhorn, S., et al., *The loss of compression in intramedullary ankle Arthrodesis using two different types of compression rods — A biomechanical study.* Journal of Biomechanics, 2006. **39 S1**: p. S136.
14. Pitz, M., *Compression-Aided Stability of Orthopaedic Devices*, in *BioEngineering*. 2011, The Georgia Institute of Technology: Atlanta.
15. Gil, F.J. and J.A. Planell, *Shape memory alloys for medical applications.* Proc Inst Mech Eng H, 1998. **212**(6): p. 473-88.
16. El Feninat, F., et al., *Shape memory materials for biomedical applications.* Adv. Eng. Mater., 2002. **4**(3): p. 91-104.
17. Machado, L.G. and M.A. Savi, *Medical applications of shape memory alloys.* Braz J Med Biol Res, 2003. **36**(6): p. 683-91.
18. Berson, L., W.C. McGarvey, and T.O. Clanton, *Evaluation of compression in intramedullary hindfoot arthrodesis.* Foot Ankle Int, 2002. **23**(11): p. 992-5.
19. Scranton, P.E., Jr., *Use of internal compression in arthrodesis of the ankle.* J Bone Joint Surg Am, 1985. **67**(4): p. 550-5.